Probiotics for Gastrointestinal Infections
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As probiotics becomes increasingly common in medical literature, pediatricians may be facing questions from parents about their use in children.

These dietary supplements are living microorganisms that change the microbial flora of the gut or another mucosal surface. Within the past 15 years, scientists have begun to study specific probiotic organisms in earnest. While many health benefits have been ascribed to probiotics, the most convincing are in the treatment of certain types of infectious diarrhea. We have recently reviewed the use of probiotics in the management of infectious diseases (Alvarez M, Oberhelman RA. Probiotic agents and infectious diseases: A modern perspective on a traditional therapy. Clin Infect Dis 32:1567-76, 2001).

The most commonly used probiotic organisms are certain strains of *Lactobacillus*; *Saccharomyces boulardii*, a nonpathogenic yeast related to (but not the same as) baker's yeast; and *Bifidobacterium*, a genus of anaerobic gram-positive rods that can constitute up to 99% of the fecal flora in exclusively breast-fed infants.

Probiotics are different from prebiotics, a new term used for non-digestible food ingredients that promote the growth of beneficial bacteria in the gastrointestinal tract. Prebiotics usually are complex oligosaccharides, and they are sold commercially (primarily in Europe and Japan) as food supplements for infants and adults.

Recent studies demonstrate that not all *Lactobacillus* strains are effective probiotics. Most probiotics studied are selected for characteristics such as ability to colonize and adhere to the gut mucosa, production of antimicrobial substances, and ability to stimulate mucosal immunity *in vitro.*

The most widely studied probiotic organism is *Lactobacillus casei* (or *L. rhamnosus*) strain GG (LGG), although other strains of *L. reuteri* and *L. acidophilus* also have been studied and found to be effective in some clinical trials. Interestingly, lactose fermentation by probiotic organisms to aid in digestion of sugars does not appear to be a major mechanism of action, since many of the most effective probiotic agents are poor lactose fermenters.

Promising clinical trial results
Controlled clinical trials from many countries have shown that LGG and similar probiotics shorten the duration of watery diarrhea, especially watery diarrhea due to rotavirus. The greatest benefit has been shown in studies from northern European countries in which 60% to 90% of cases were associated with rotavirus.

In developing countries where rotavirus accounts for a much smaller proportion of cases and where bacterial and parasitic agents are more common, probiotics only demonstrate a benefit in the subgroups with watery diarrhea (i.e., no benefit from probiotic treatment was seen in cases of invasive or bloody diarrhea). While most clinical trials only have included hospitalized inpatients with diarrhea, a recent Danish study (V Rosenfeldt *et. al.*, Pediatr Infect Dis 21:417-9, 2002) also demonstrated benefit from LGG treatment in outpatients with milder diarrhea recruited from a child care center.

Several smaller studies also have shown a benefit from LGG and *S. boulardii* treatment of antibiotic-associated diarrhea and relapsing diarrhea due to *Clostridium difficile*, but data do not suggest that probiotics are effective against specific pathogens other than rotavirus and *C. difficile.*

A recent meta-analysis pooled the results of eight placebo-controlled trials, including 731 children with diarrhea who took a variety of probiotic agents (Szajewska H and Mrukowicz JZ. *J Pediatr Gastroenterol Nutr.* 2001;33:S17-S25). The pooled relative risk of diarrhea in the probiotic group was 0.43. These studies mostly were of rotaviral diarrhea, and LGG was the only probiotic agent with sufficient data to demonstrate a consistent effect on reduction of diarrhea in this analysis.

Studies of probiotics for treatment of traveler's diarrhea in adults and for prevention of diarrhea in children have shown modest benefits in some cases, but it is difficult to make generalizations about these potential uses because of the limited number of studies and differences in the study populations. In a randomized placebo controlled trial in 204 undernourished children receiving LGG or PL in liquid gelatin 6 days a week for 15 months, there were significantly fewer diarrheal episodes the in LGG group (5.2 vs. 6.0 episodes/child/yr. [e/c/y], p=0.028). The greatest difference was seen in 18-29 month old group (p=0.004) but the effect was primarily limited to non-breastfed children (BF: 6.6 e/c/y LGG vs. 6.3 e/c/y PL, N.S.; NBF: 4.7 e/c/y LGG vs. 5.9 e/c/y PL, p=0.005) [Oberhelman et. al.; J Pediatr 1999; 134: 15-20].

A small number of studies also have shown some benefit from treatment with several *Lactobacillus* strains in women with recurrent *Candida* vaginitis. Future applications under investigation are treatment of bacterial vaginosis, mucosal vaccine development, prevention of HIV and STD transmission in women, control of inflammation and inflammatory bowel disease, and treatment of multidrug-resistant organisms on body surfaces.

Probiotics in pediatrics

What do these studies mean for pediatricians practicing in the United States? First, it is important to educate parents that these studies were done with scientifically selected strains, so one would not expect to see the same benefit from commercially produced yogurt from the grocery store.

Scientifically tested probiotic agents marketed commercially in the United States include LGG (Culturelle; CAG Functional Foods) and *S. boulardii* (Florastor; Biocodex Inc.). Many probiotic products are sold on the Internet by various vendors, but quality control of these products is variable. The probiotic strains studied are more widely available in Europe and the Far East, where they are marketed in a variety of ways (e.g., as food supplements for infant formula, commercial yogurt and lyophilized powder capsules). Probiotics usually are distributed over-the-counter and dosing is frequently not well standardized.

Second, probiotic organisms are generally recognized as benign and are thought to be safe, although as food supplements they have not been subjected to the rigorous safety studies and manufacturing standards required for drugs. Independent microbiologic analyses have not always identified the ingredients listed on the label, and other quality control problems reported (mostly in products made outside the United States) are inconsistent numbers of microorganisms and presence of potential pathogens such as *Enterococcus faecium.* While there are several reports of opportunistic infections with *Lactobacilli* in the medical literature (mostly in patients with underlying diseases), there have been no increases in cases of *Lactobacillus* bacteremia in countries like Finland where probiotic use and surveillance for probiotic-associated infection are common. Only a handful of studies have evaluated the safety and efficacy of probiotics in HIV-infected individuals. Although these have not demonstrated adverse effects in a small number of HIV-positive persons treated with *Lactobacillus reuteri* and *Saccharomyces boulardii*, more data will be needed before wider use in this population can be promoted.

There are data to support the use of effective probiotics for watery-diarrhea, especially if it is known to be rotaviral, and perhaps in some cases of antibiotic-associated diarrhea or relapsing *C. difficile* colitis. However, we do not have sufficient data to clearly define the role that these products should play in general pediatric practice. Further studies to evaluate the efficacy of probiotics in outpatients are needed. With time probiotics likely will be more readily available, and physicians and patients should learn how these products can be used most effectively.

Future research needs in the area of probiotics in diarrheal diseases include:
•Studies of the effects of repetitive probiotic therapy on long term growth and development. To date most studies have focused on the effect on single diarrheal episodes, which does not allow detection of long term effects on nutritional status that may be significant.

•Further studies of safety issues

•Better understanding of the physiology of probiotic organisms and mechanisms of protection

•Better understanding of the role of malnutrition, lactose intolerace, and breastfeeding as cofactors that impact probiotic efficacy